

Claims

1. A mouse comprising a transgene comprising (i) a regulatory gene encoding a regulatory protein, and (ii) a transcription terminator at which site transcription terminates, wherein said transgene has integrated into an endogenous gene of said mouse such that said regulatory gene is positioned for expression under control of the promoter of said endogenous gene, said promoter being operably linked to said regulatory gene upon integration of said transgene into said endogenous gene, and said transcription terminator mutagenizes said endogenous gene.

2. The mouse of claim 1, wherein said transgene further comprises a splice acceptor.

3. The mouse of claim 1, wherein said transgene further comprises retroviral packaging and integration sequences.

4. The mouse of claim 3, wherein said retroviral packaging and integration sequences are from a Moloney murine leukemia virus sequence.

5. The mouse of claim 1, wherein said regulatory protein modulates the expression of another gene.

6. The mouse of claim 5, wherein said regulatory protein is a tetracycline repressor fused to an activator protein.

7. The mouse of claim 6, wherein said activator protein is VP16.

8. The mouse of claim 1, wherein said transgene further comprises a nucleic acid

sequence encoding a constitutively expressed marker gene, said marker gene encoding a marker protein that is detectable in a mammalian cell.

5 9. The mouse of claim 8, wherein said marker protein is a green fluorescent protein.

10 10. The mouse of claim 9, wherein said green fluorescent protein has increased cellular fluorescence relative to the wild-type green fluorescent protein.

10 11. The mouse of claim 9, wherein the green fluorescent protein is fused to a mammalian selectable marker protein.

15 12. The mouse of claim 11, wherein said mammalian selectable marker is neomycin phosphotransferase.

15 13. The mouse of claim 1, wherein said transgene further comprises a recognition sequence recognized by a yeast VDE DNA endonuclease.

20 14. The mouse of claim 1, further comprising a second transgene comprising a gene operably linked to regulatory sequence regulated by said regulatory protein, wherein said second transgene is integrated into the genome of said mouse.

15. A cell comprising:

25 (a) a first transgene comprising (i) a regulatory gene encoding a regulatory protein and (ii) a transcription terminator at which site transcription terminates, wherein said transgene is integrated into an endogenous gene of said cell such that said regulatory gene is positioned for expression under control of the promoter of said endogenous gene,

said promoter being operably linked to said regulatory gene upon integration of said transgene into said endogenous gene, and said transcription terminator mutagenizes said endogenous gene; and

(b) a second transgene comprising a gene operably linked to regulatory sequence regulated by said regulatory protein, wherein said second transgene is integrated into the genome of said cell.

16. A pair of mice comprising:

(a) a first mouse comprising a first transgene comprising (i) a regulatory gene encoding a regulatory protein and (ii) a transcription terminator at which site transcription terminates, wherein said first transgene has integrated into an endogenous gene of said mouse such that said regulatory gene is positioned for expression under control of the promoter of said endogenous gene, said promoter being operably linked to said regulatory gene upon integration of said transgene into said endogenous gene, and said transcription terminator mutagenizes said endogenous gene; and

(b) a second mouse comprising a second transgene comprising a gene operably linked to regulatory sequence regulated by said regulatory protein, wherein said second transgene has integrated into the genome of said second mouse.

17. A method of producing a mouse comprising a first transgene comprising (i) a regulatory gene encoding a regulatory protein and (ii) a transcription terminator at which site transcription terminates, wherein said transgene is integrated into an endogenous gene of said mouse such that said regulatory gene is positioned for expression under control of the promoter of said endogenous gene, said promoter being operably linked to said regulatory gene upon integration of said transgene into said endogenous gene, and said transcription terminator mutagenizes said endogenous gene; and a second transgene

